

Figure 1

General Synthetic Scheme for 1,3,4-Oxadiazole Inhibitors

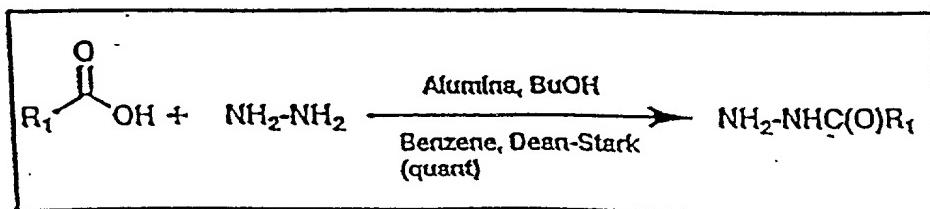
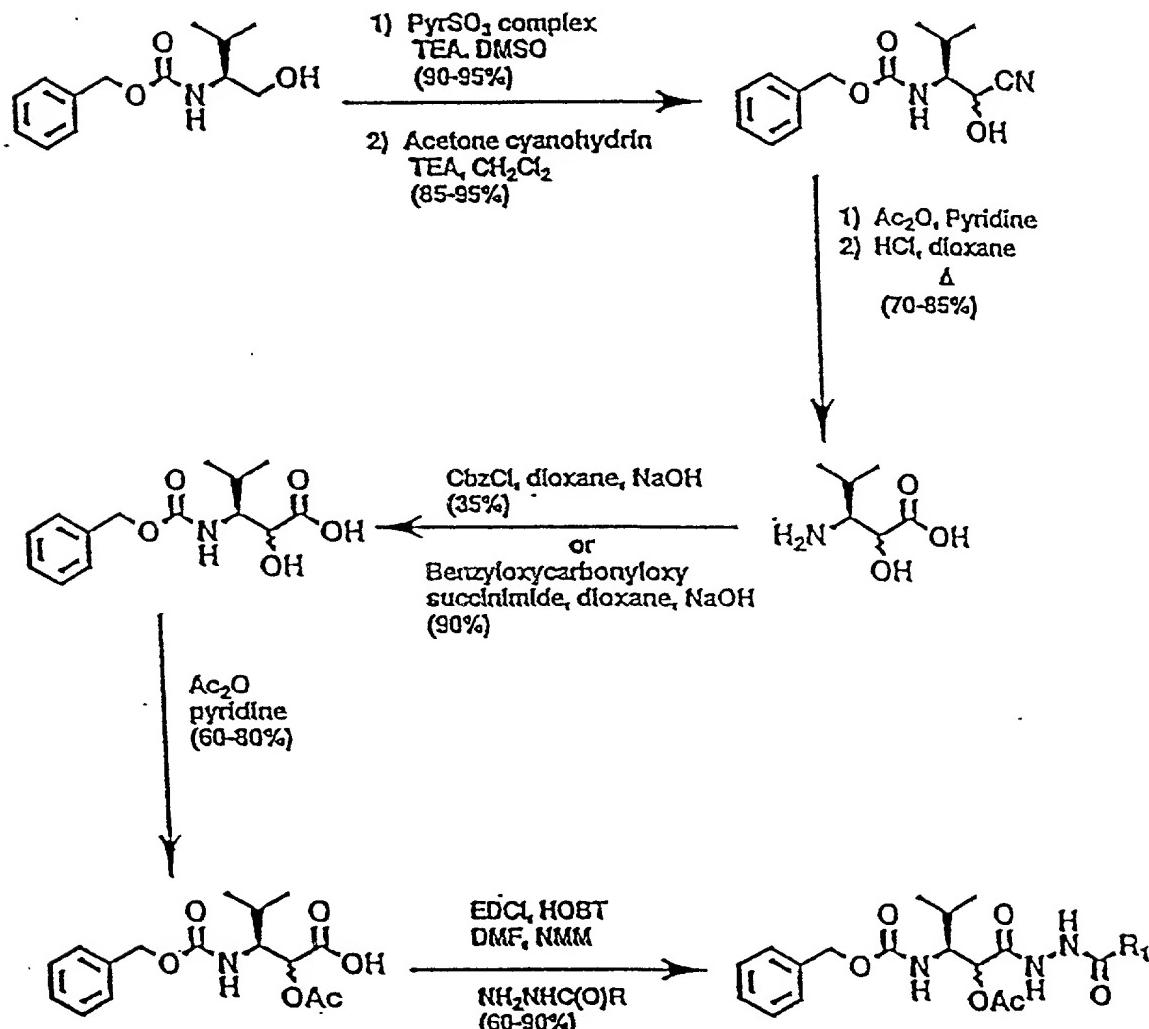


Figure 2

General Scheme for 1,3,4-Oxadiazole Inhibitors - Continued

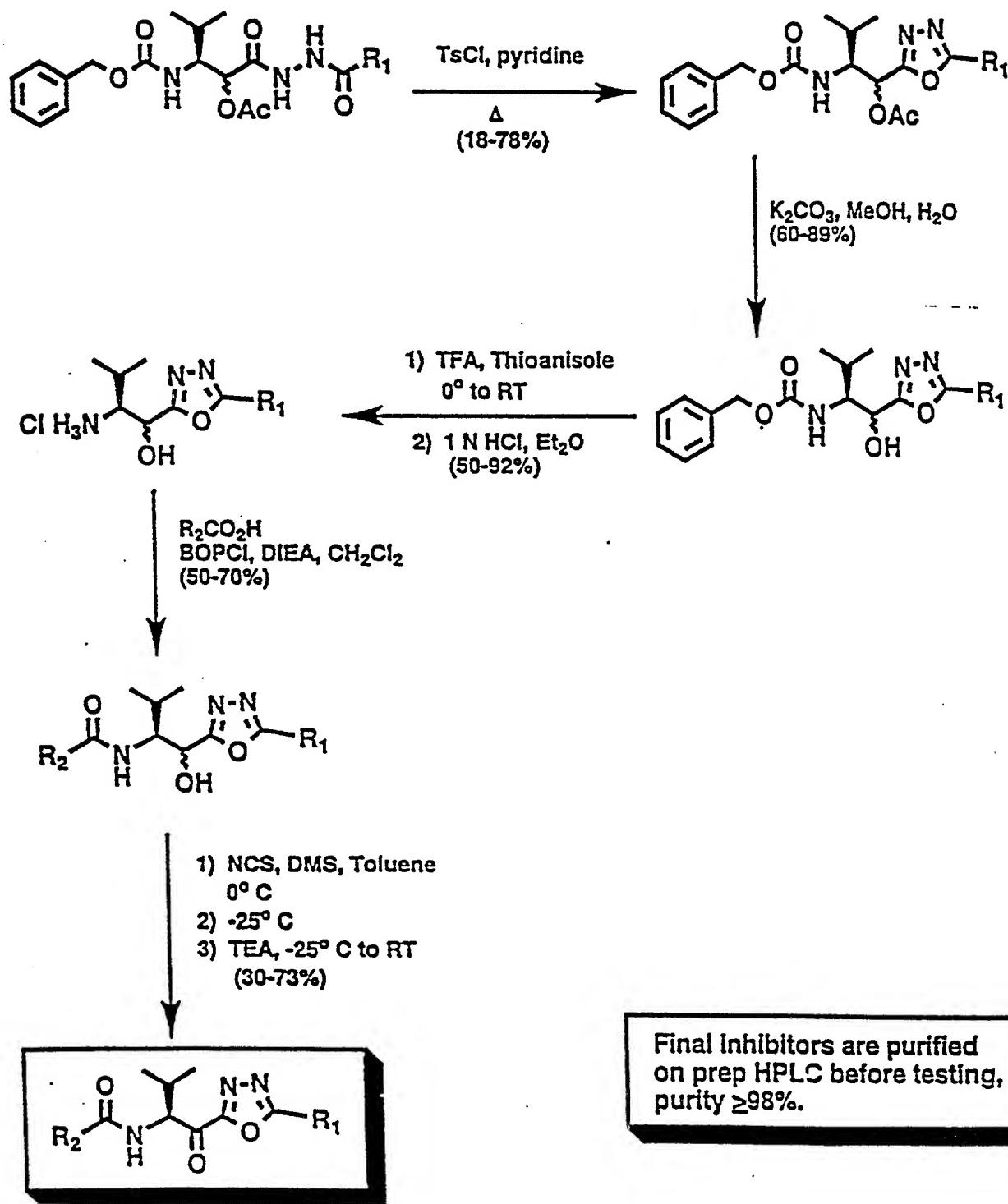


Figure 3

General Synthetic Scheme for 1,2,4-Oxadiazole Inhibitors

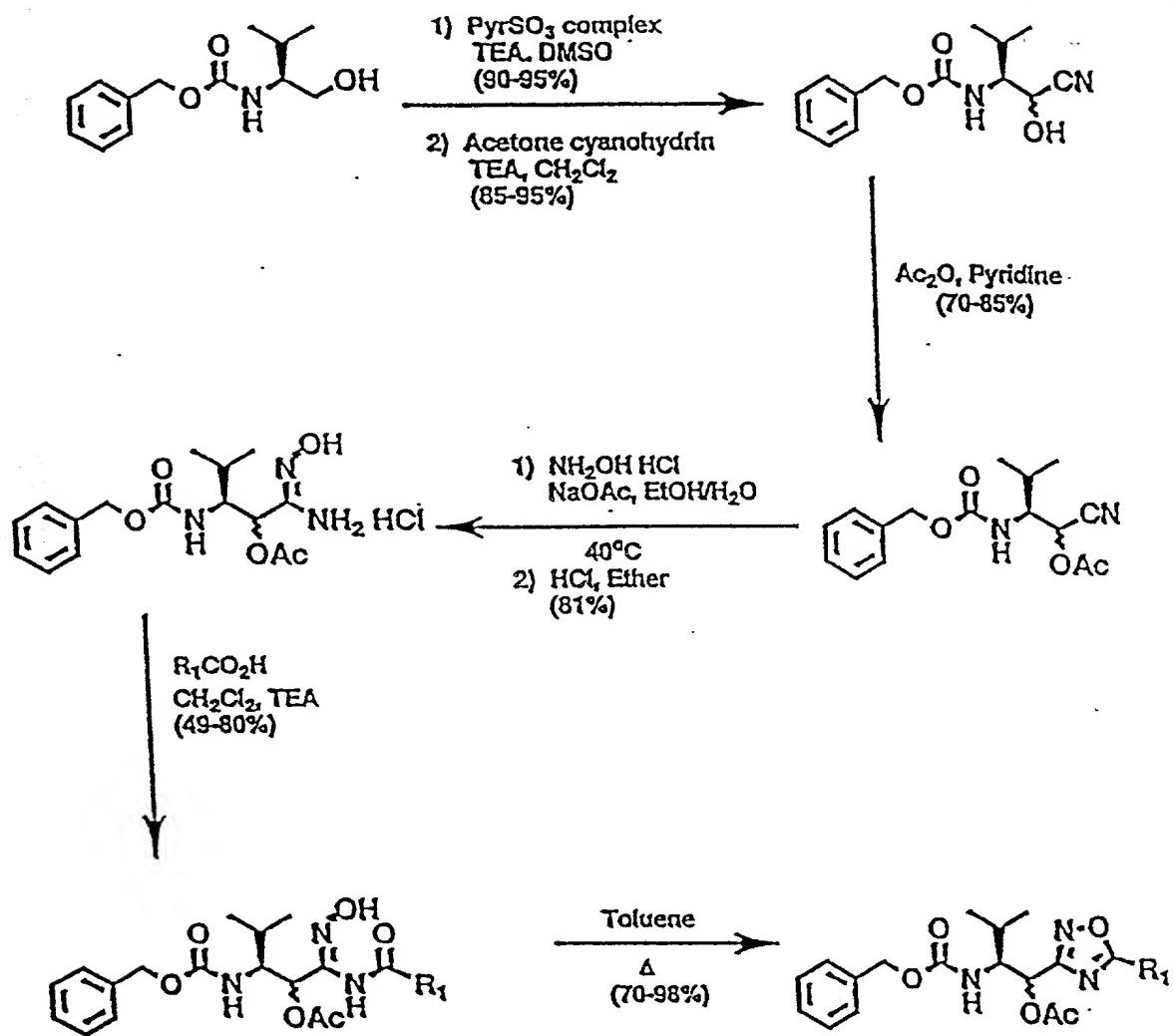


Figure 4

General Synthetic Scheme for 1,2,4-Oxadiazole inhibitors
(Continued)

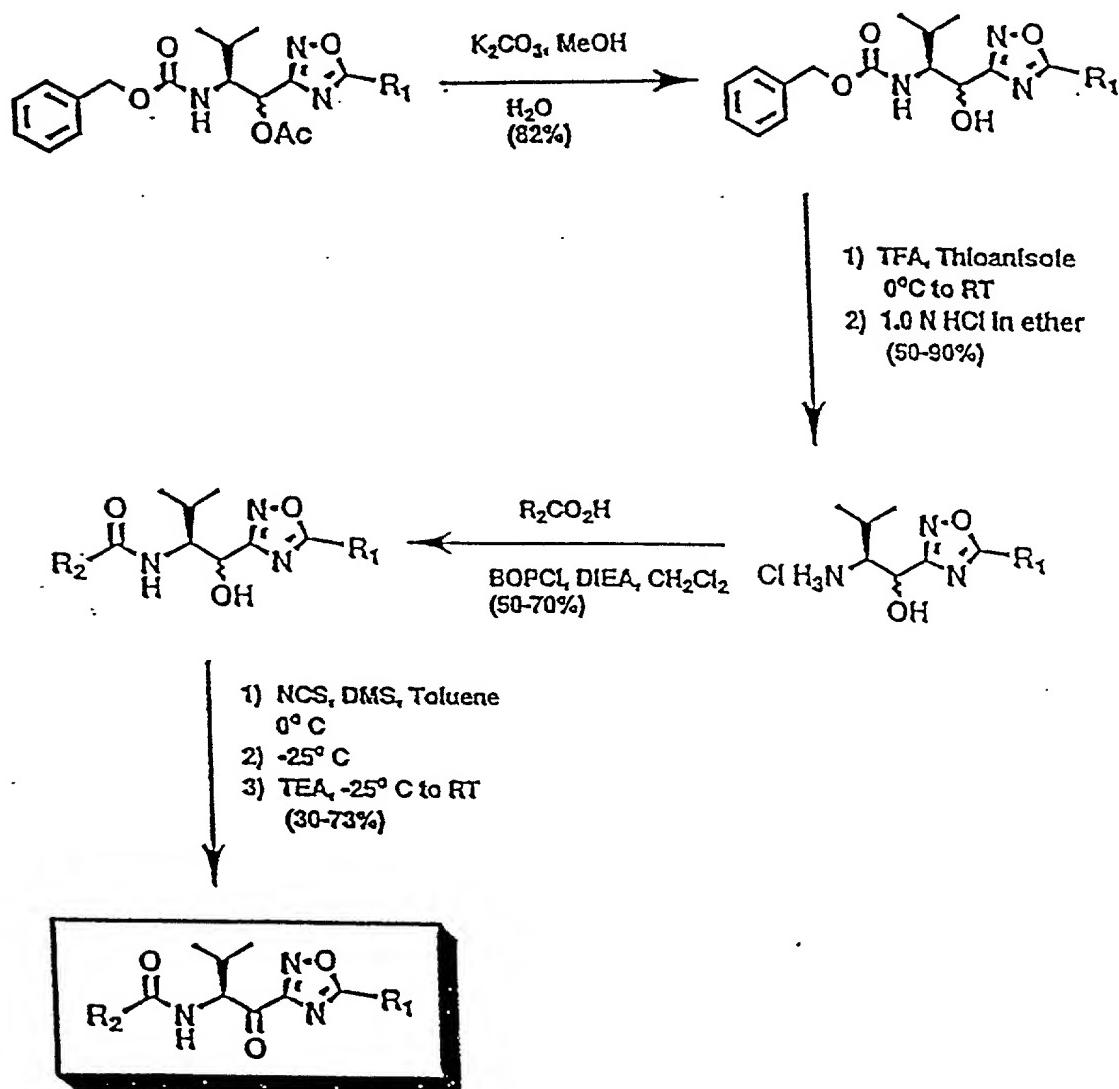


Figure 5

General Synthetic Scheme for P₂-P₃ Modified Based Inhibitors

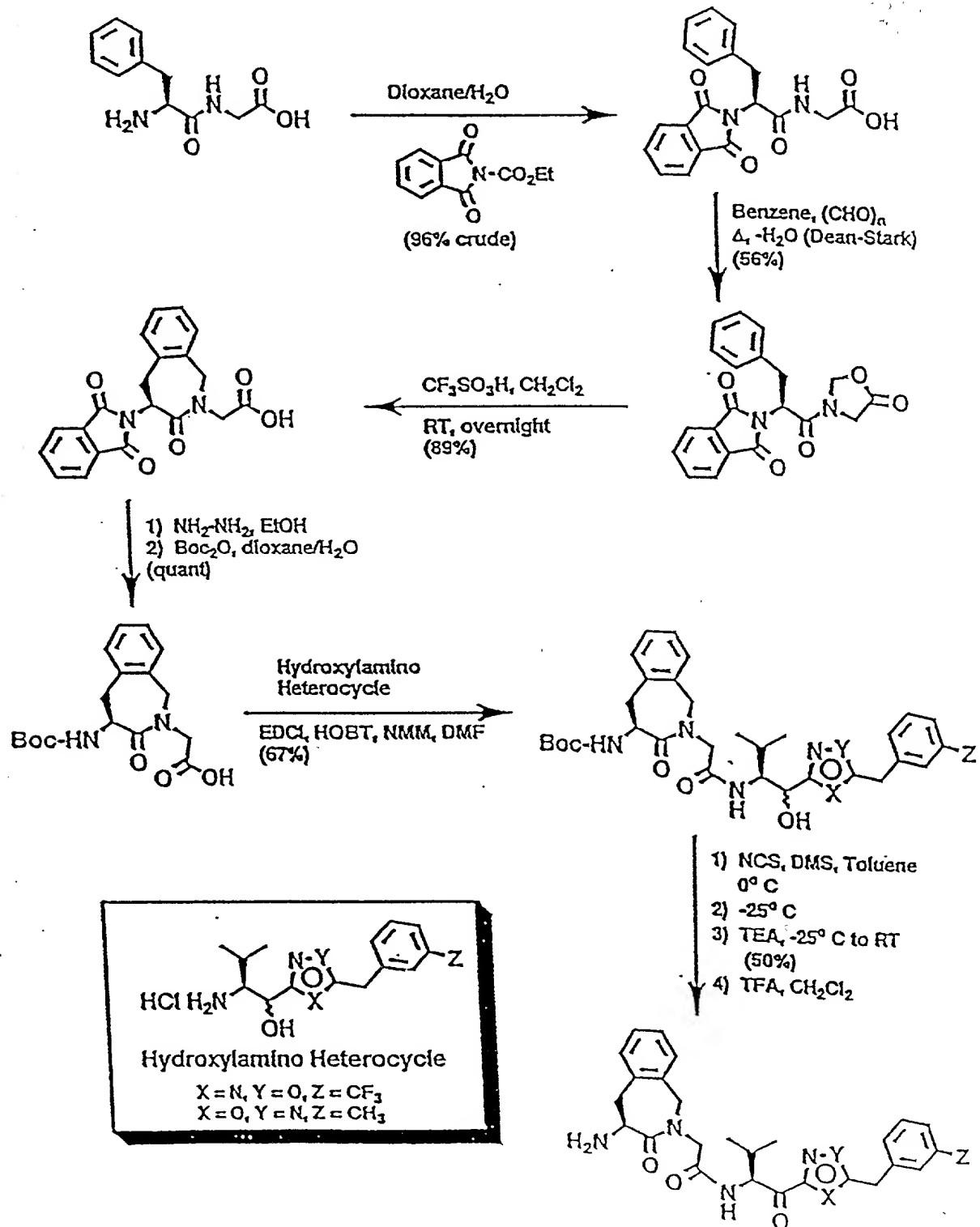


Figure 6

Synthetic Scheme for P₂-P₃ Modified Inhibitors

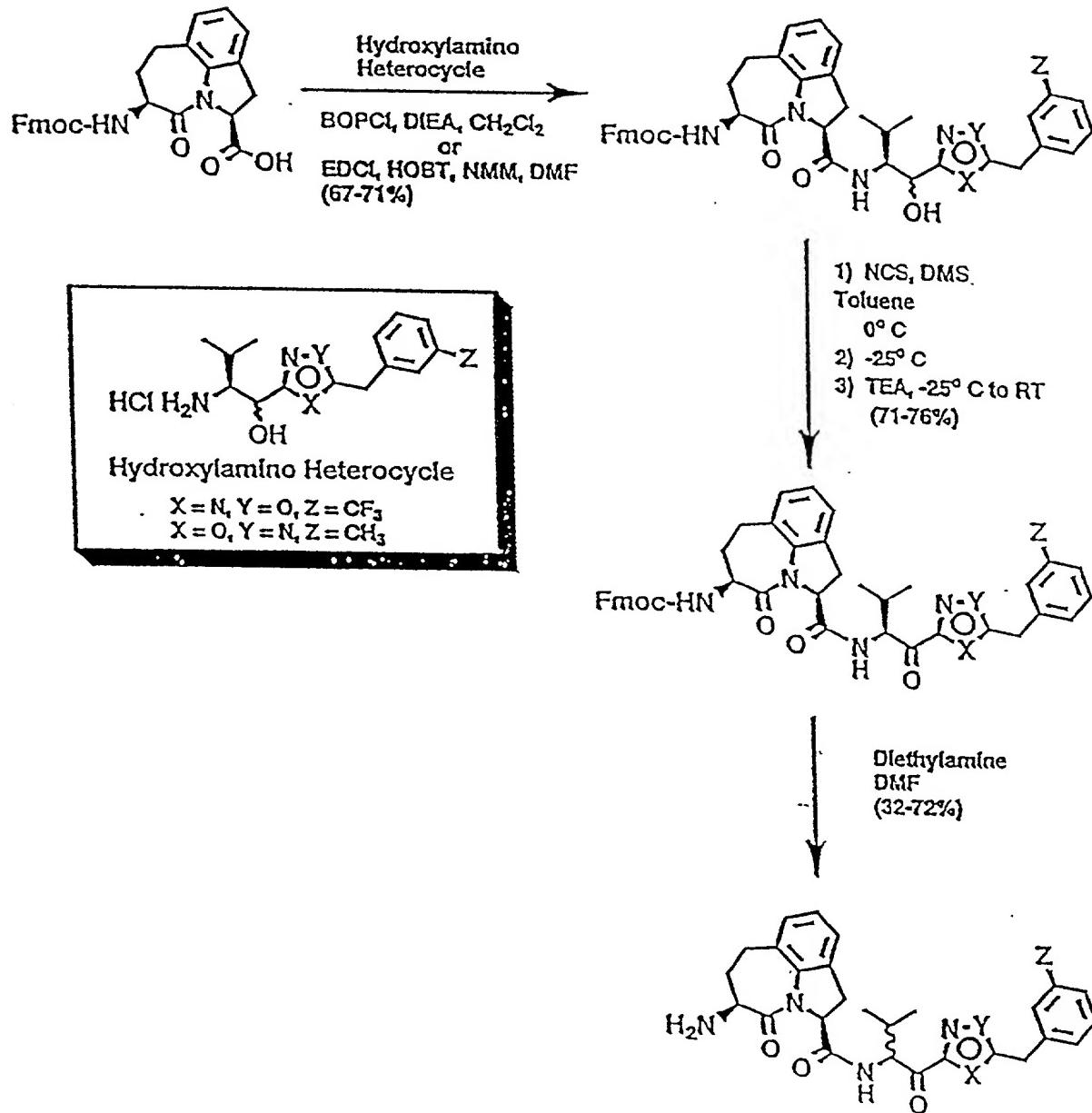


Figure 7

Synthetic Scheme for P₂-P₃ Modified Inhibitors

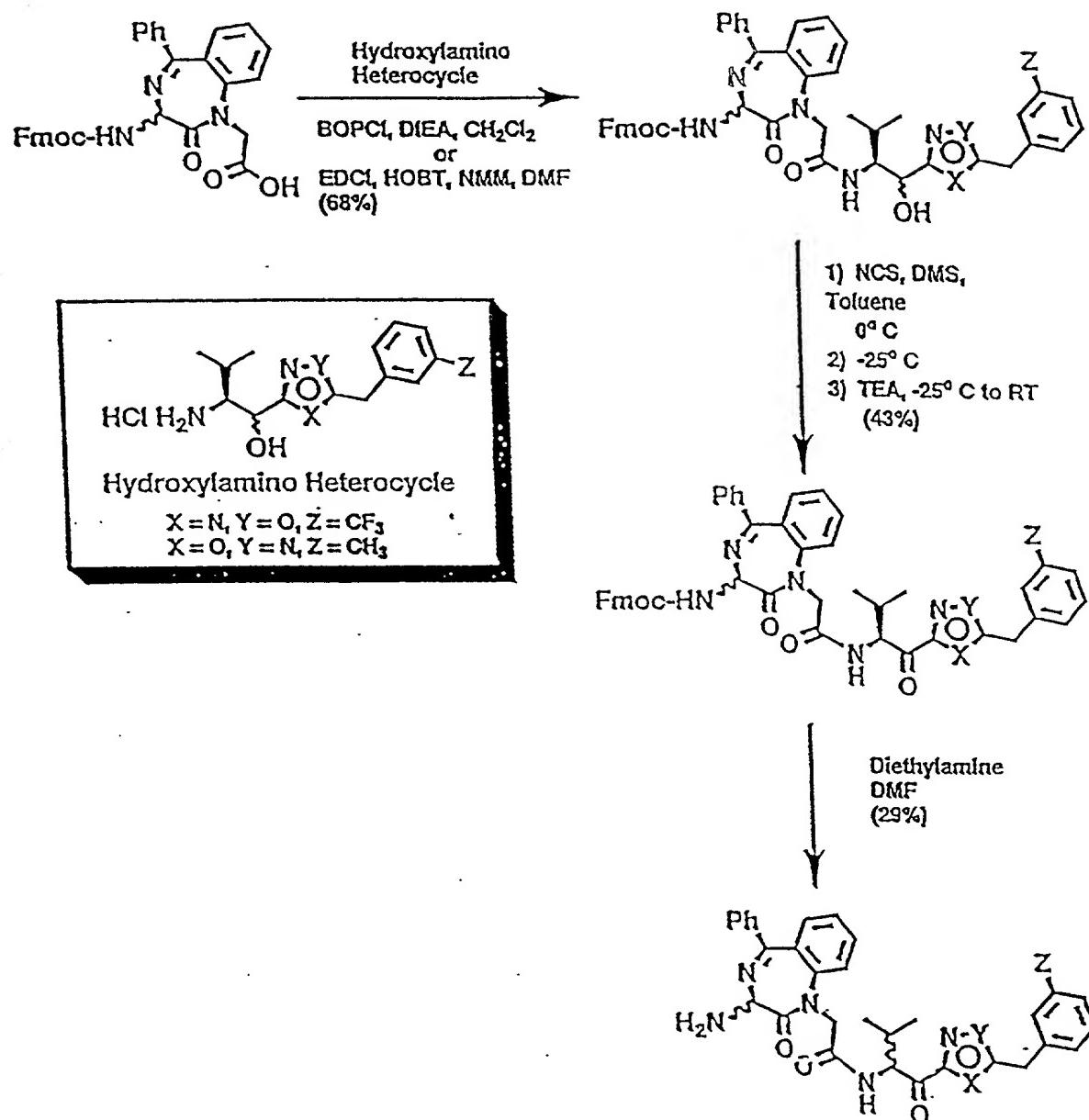


Figure 8

General Synthetic Scheme for P₂-P₃ Modified Inhibitors

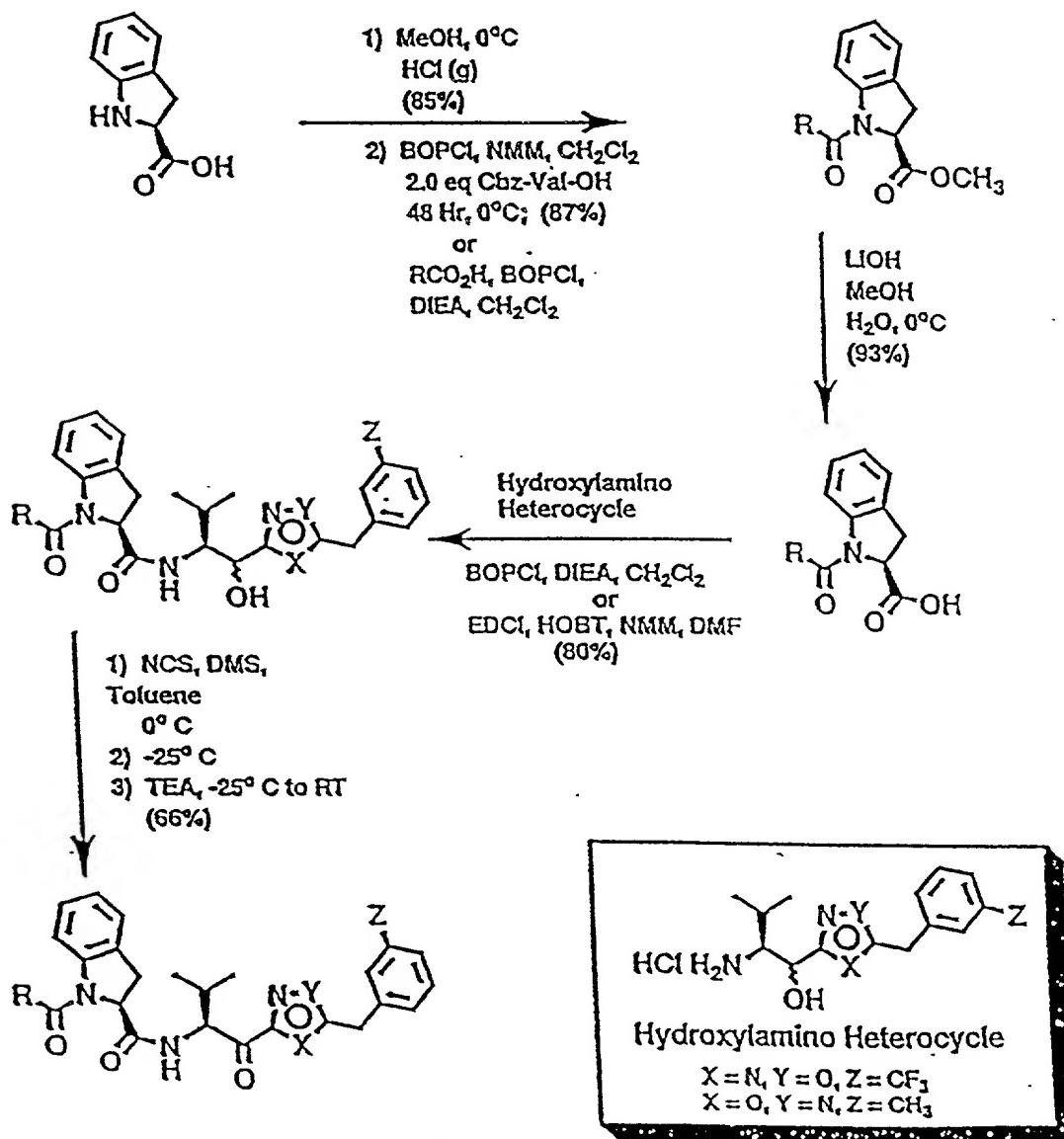


Figure 9

Synthetic Scheme for P₂-P₃ Modified Inhibitors

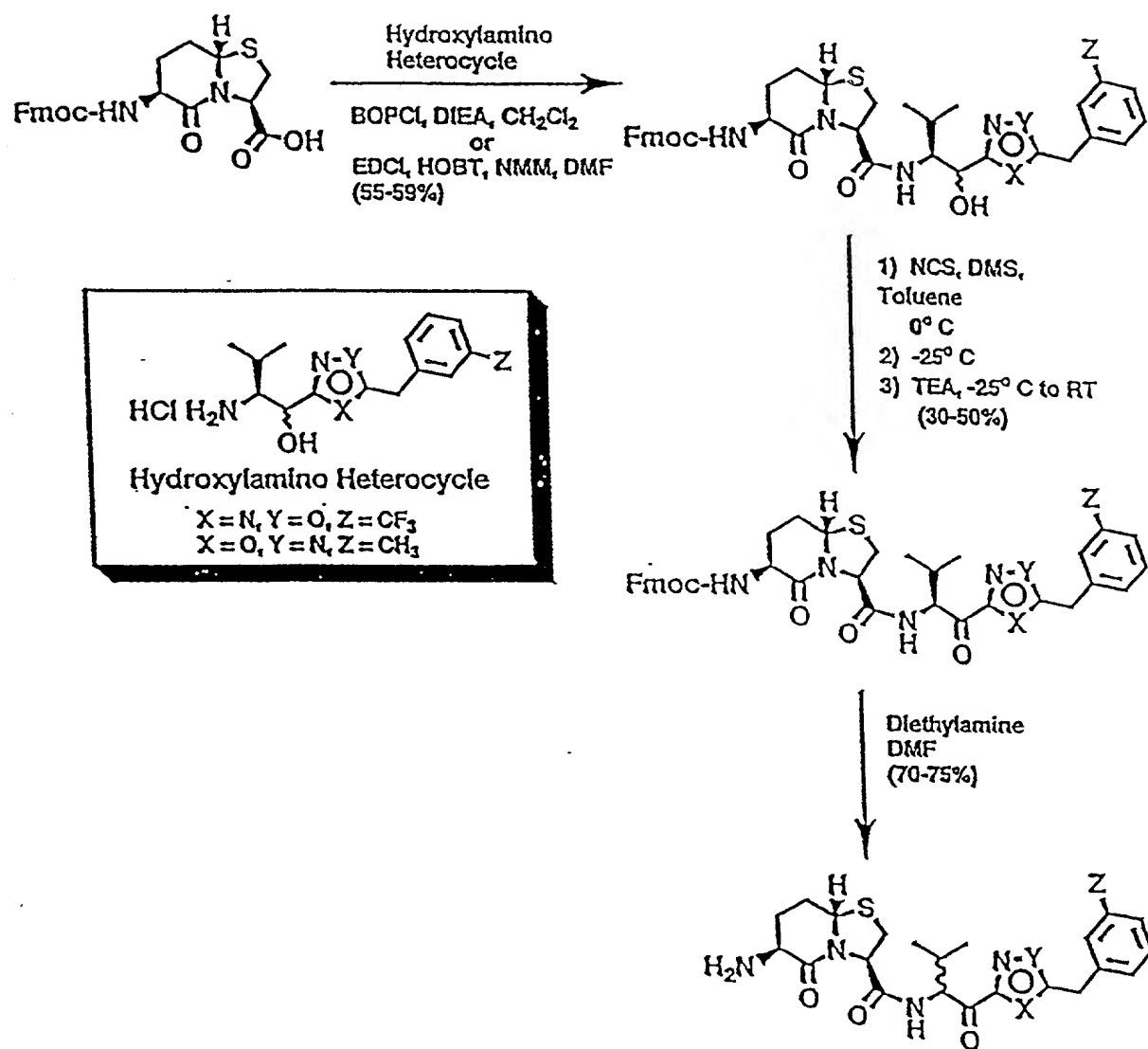


Figure 10

General Synthetic Scheme for P₂-P₃ Modified Inhibitors

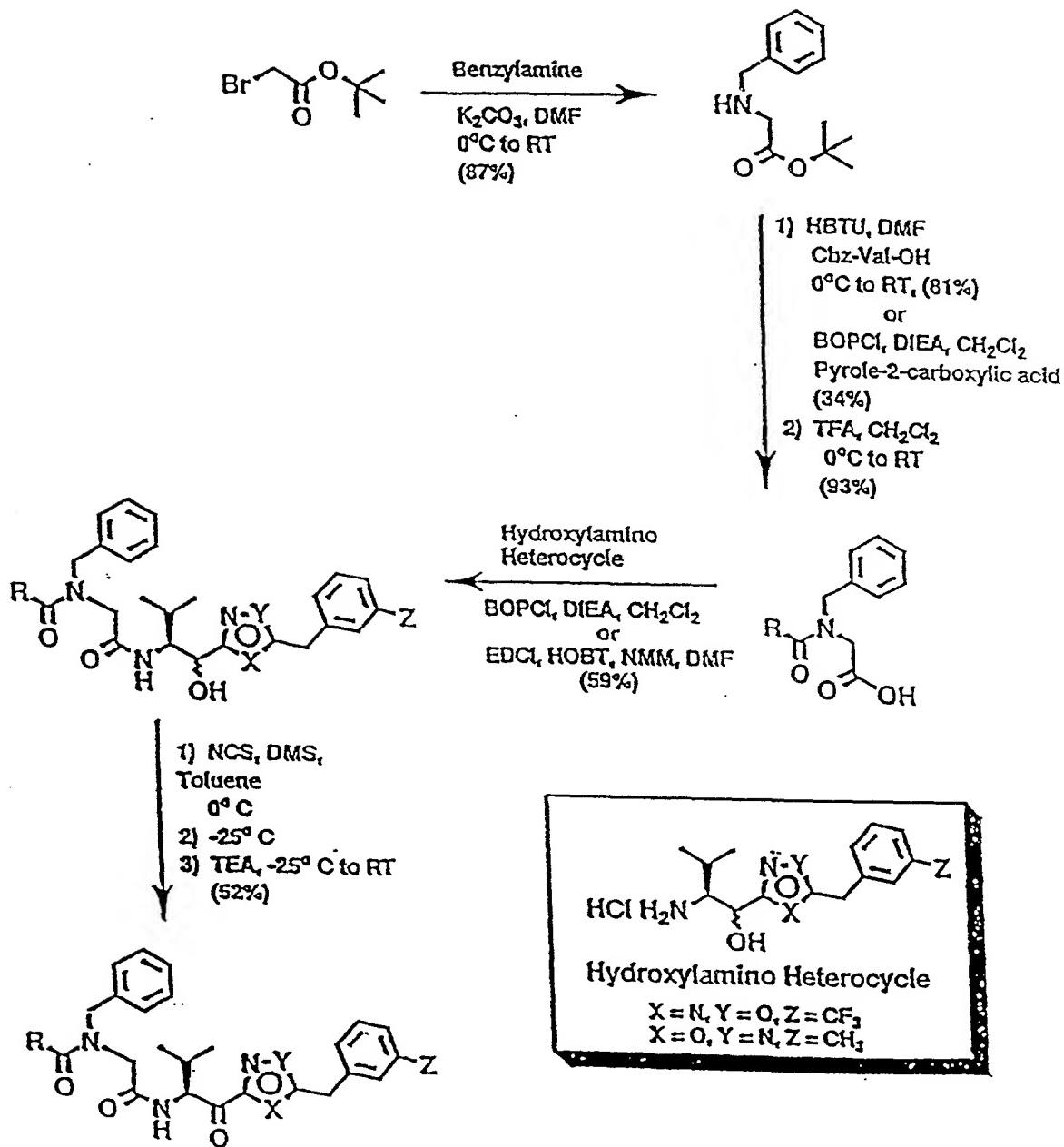


Figure 11

General Synthetic Scheme for P₂-P₃ Lactam Based Inhibitors

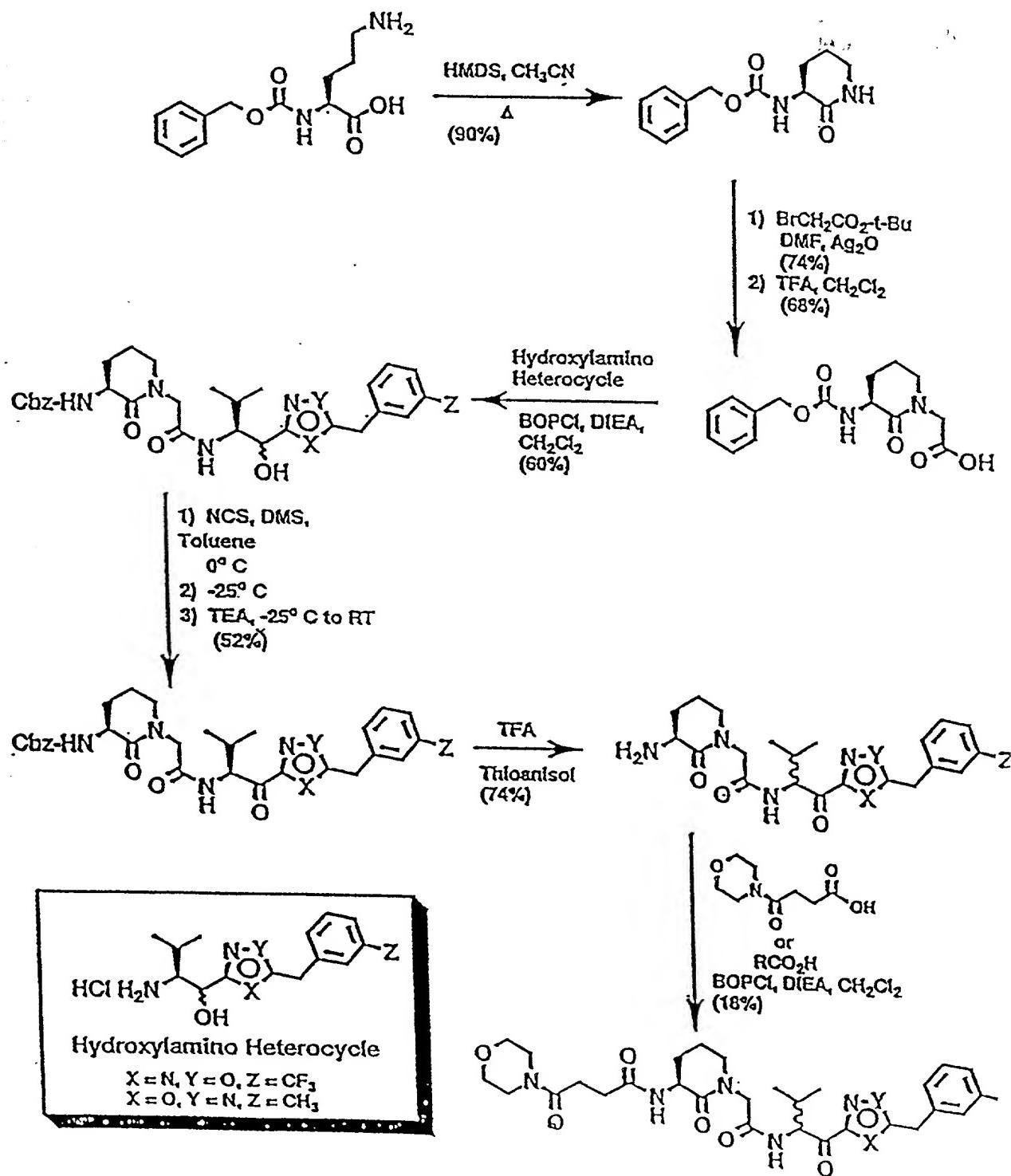


Figure 12

General Synthetic Scheme for P₂-P₃ Lactam Based Inhibitors

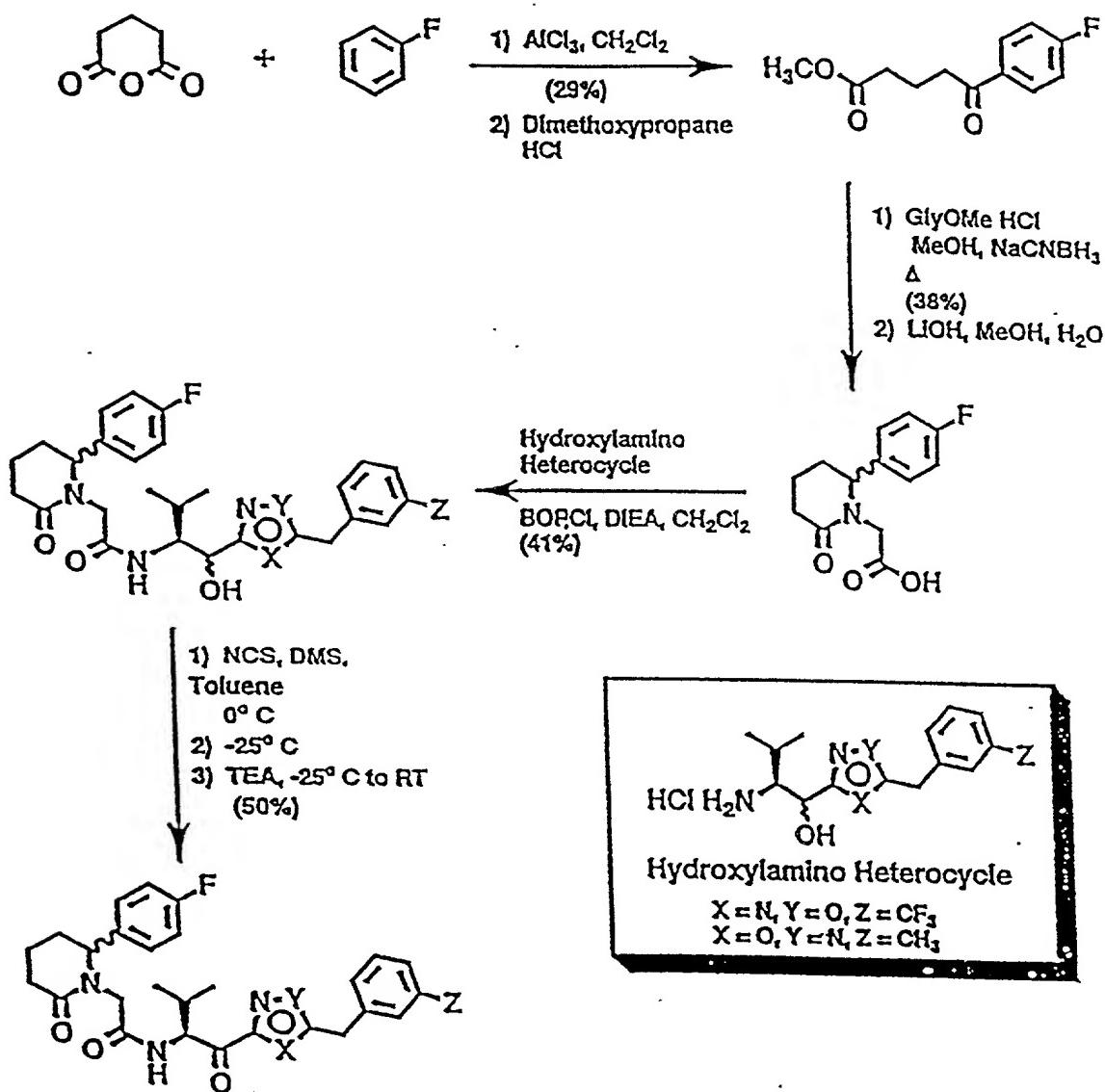


Figure 13

General Synthetic Scheme for Metathiazanone Based Inhibitors

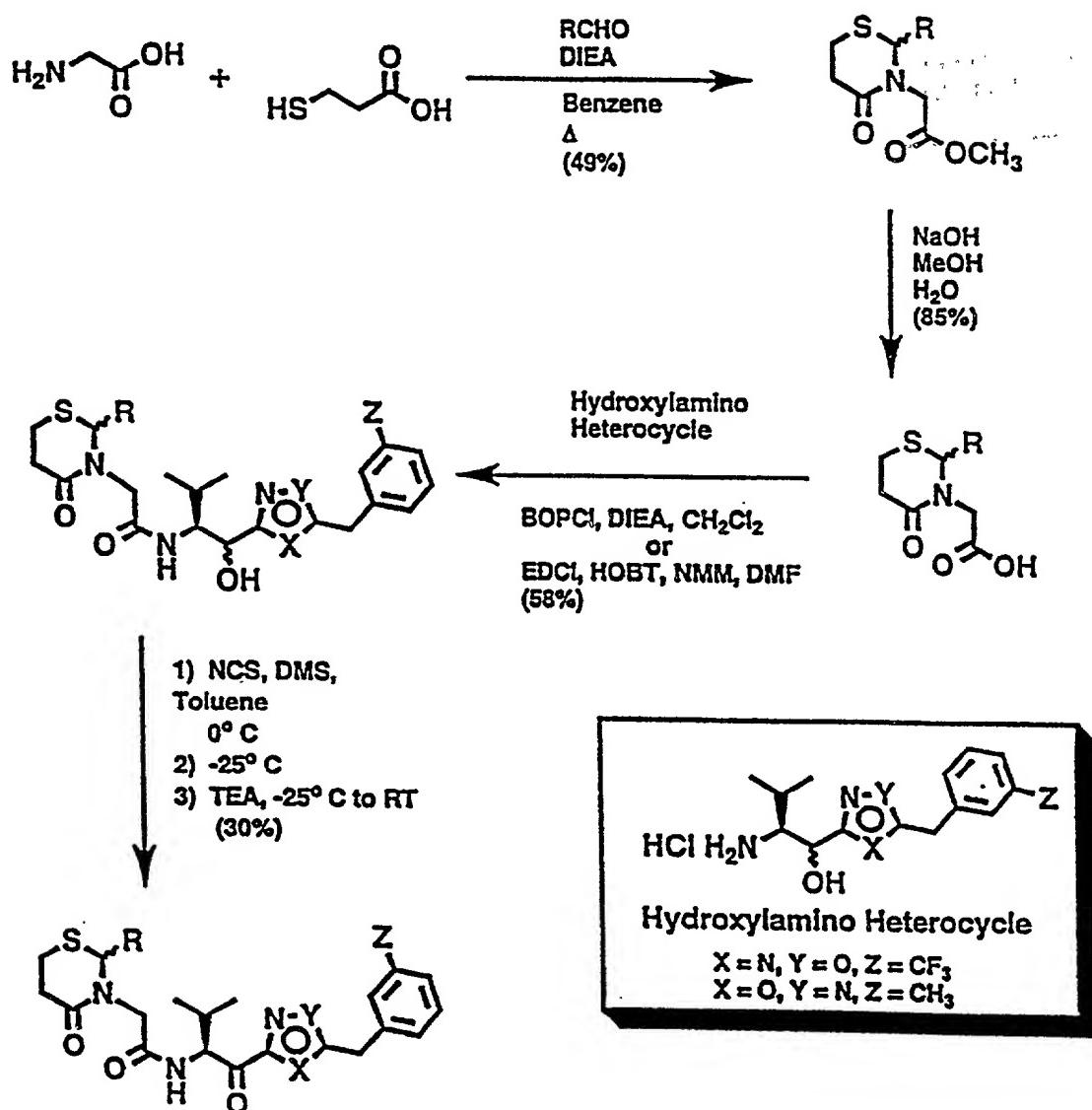


Figure 14

General Synthetic Scheme for Thiazolidinone Based Inhibitors

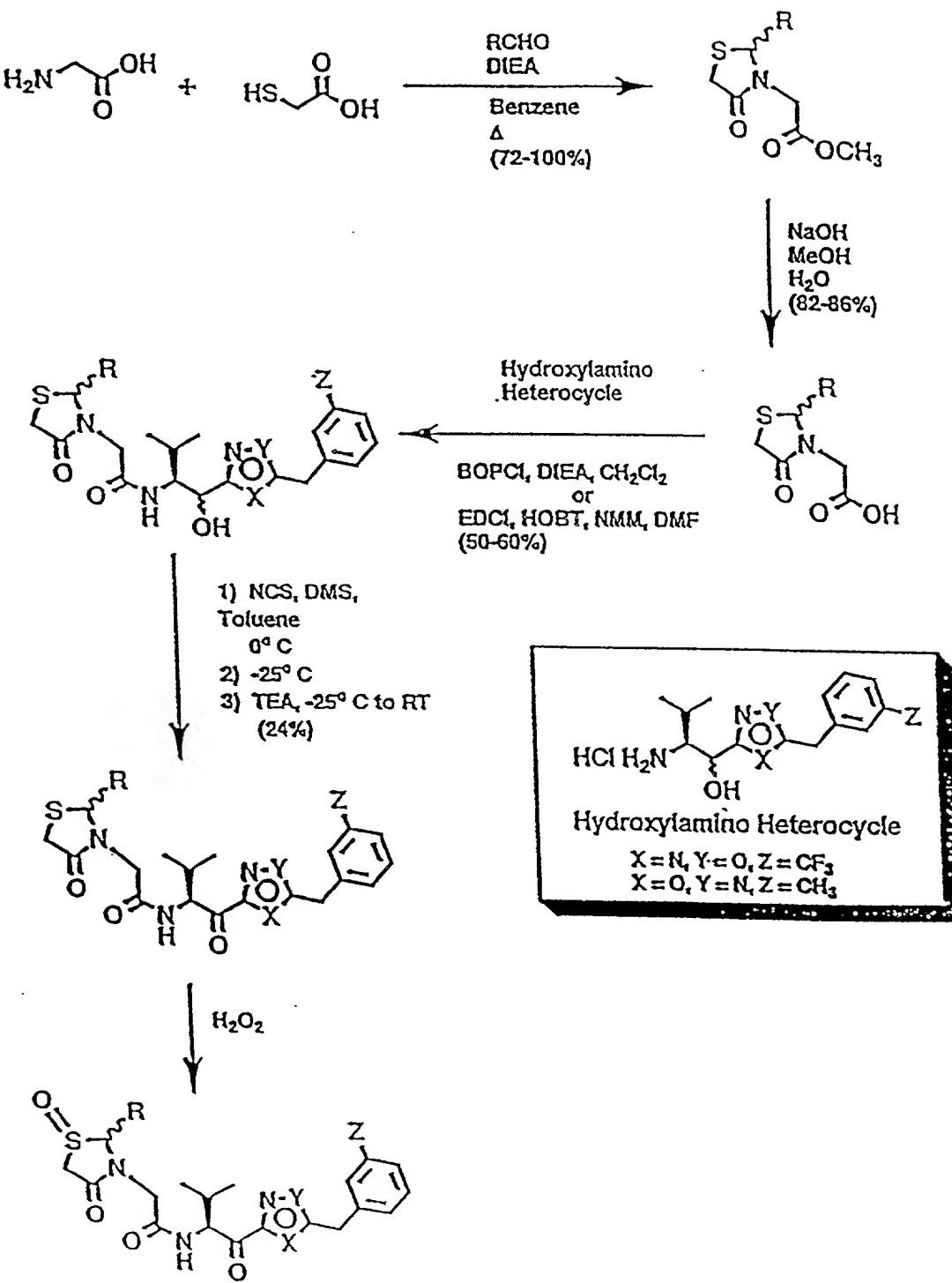


Figure 15

General Synthetic Scheme for Pyridazinedione Based Inhibitors

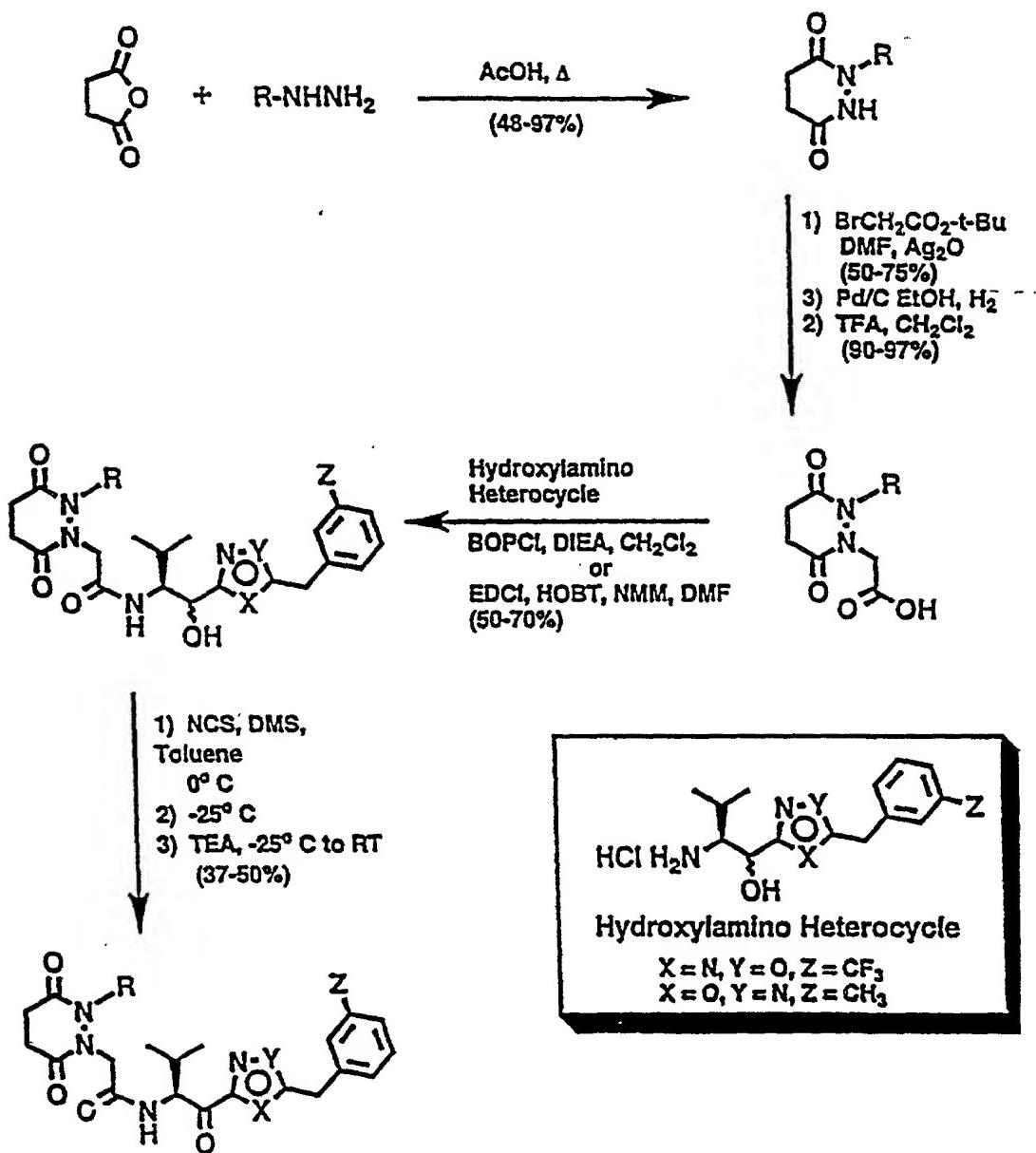


Figure 16

General Synthetic Scheme for Benzopyridazinedione Based Inhibitors

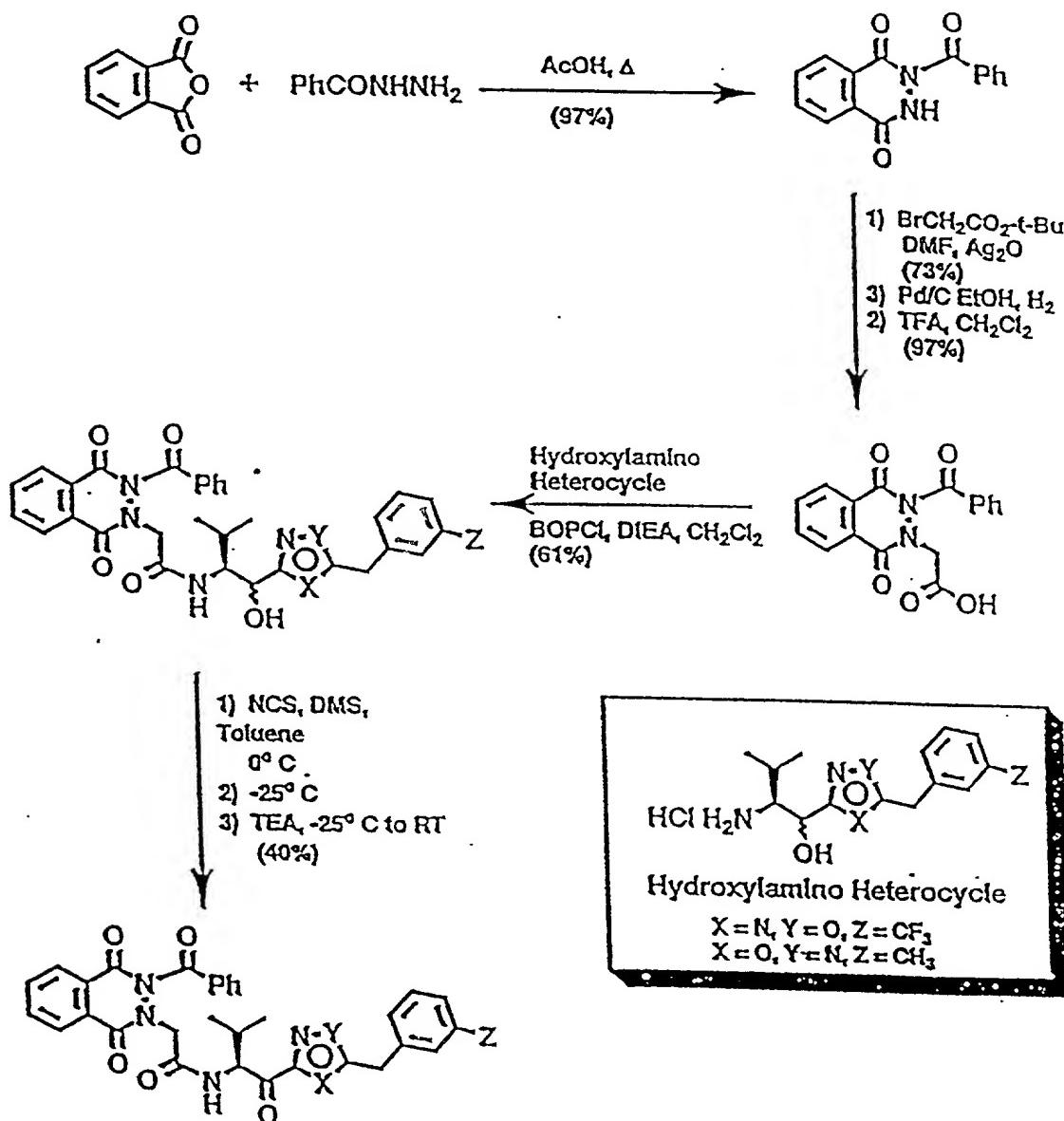


Figure 17

General Synthetic Scheme for Quinolone and N-Substituted Quinolone Based Inhibitors

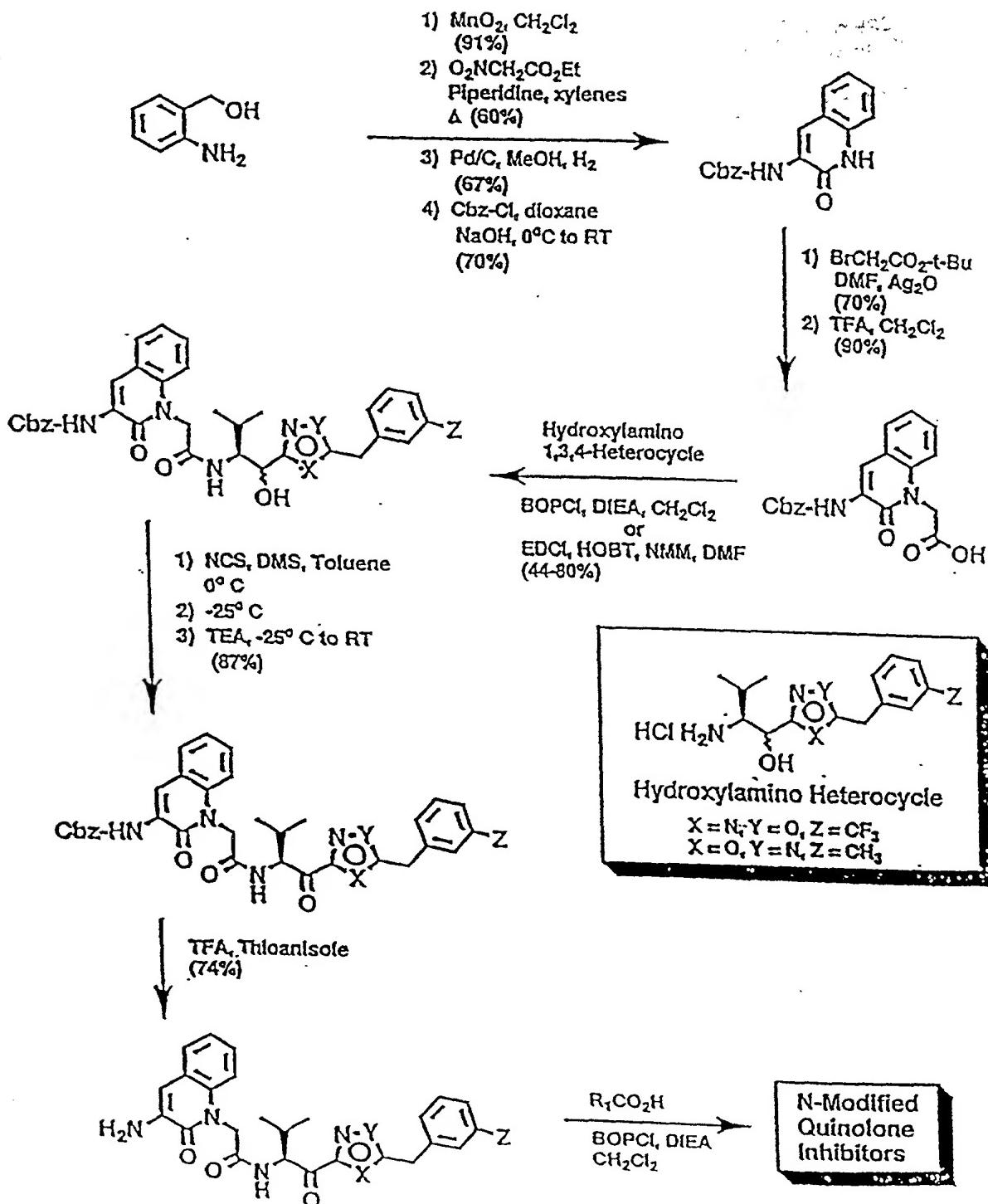


Figure 18

General Synthetic Scheme for 3,4-Dihydroquinolone Based Inhibitors

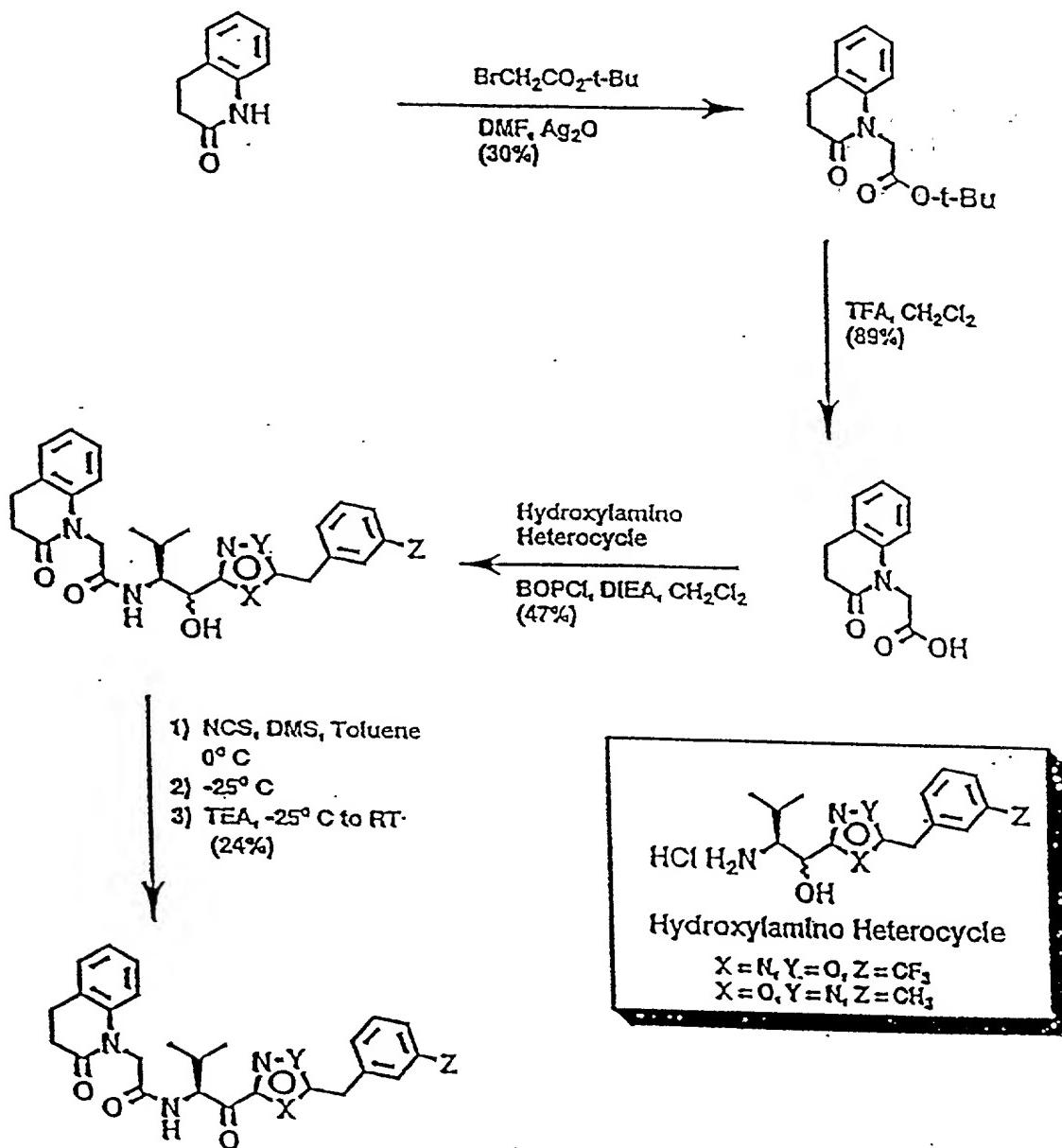


Figure 19

General Synthetic Scheme for Benzylidene Diketopiperazine Based Inhibitors

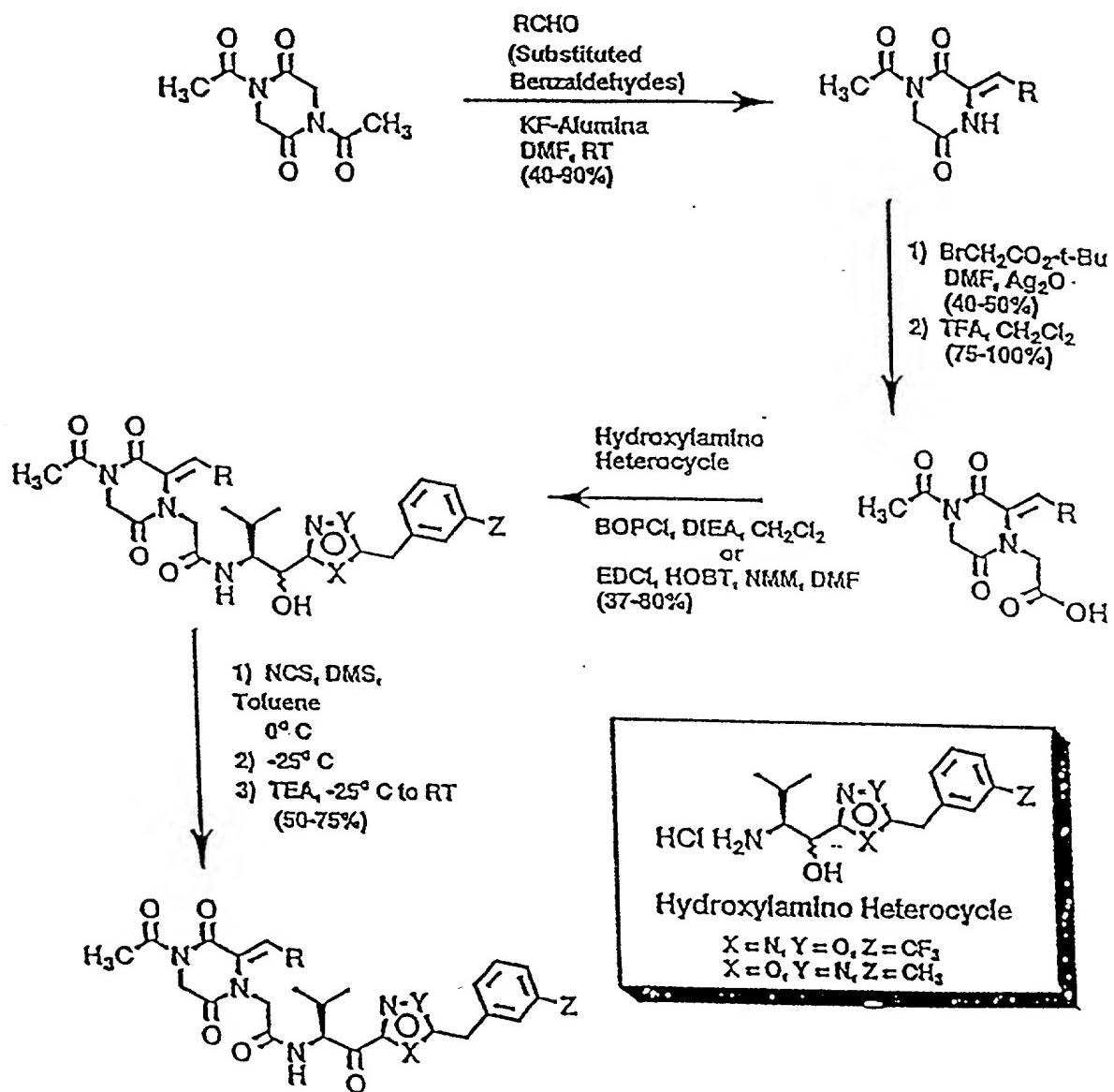


Figure 20

General Synthetic Scheme for Diketopiperazine Based Inhibitors

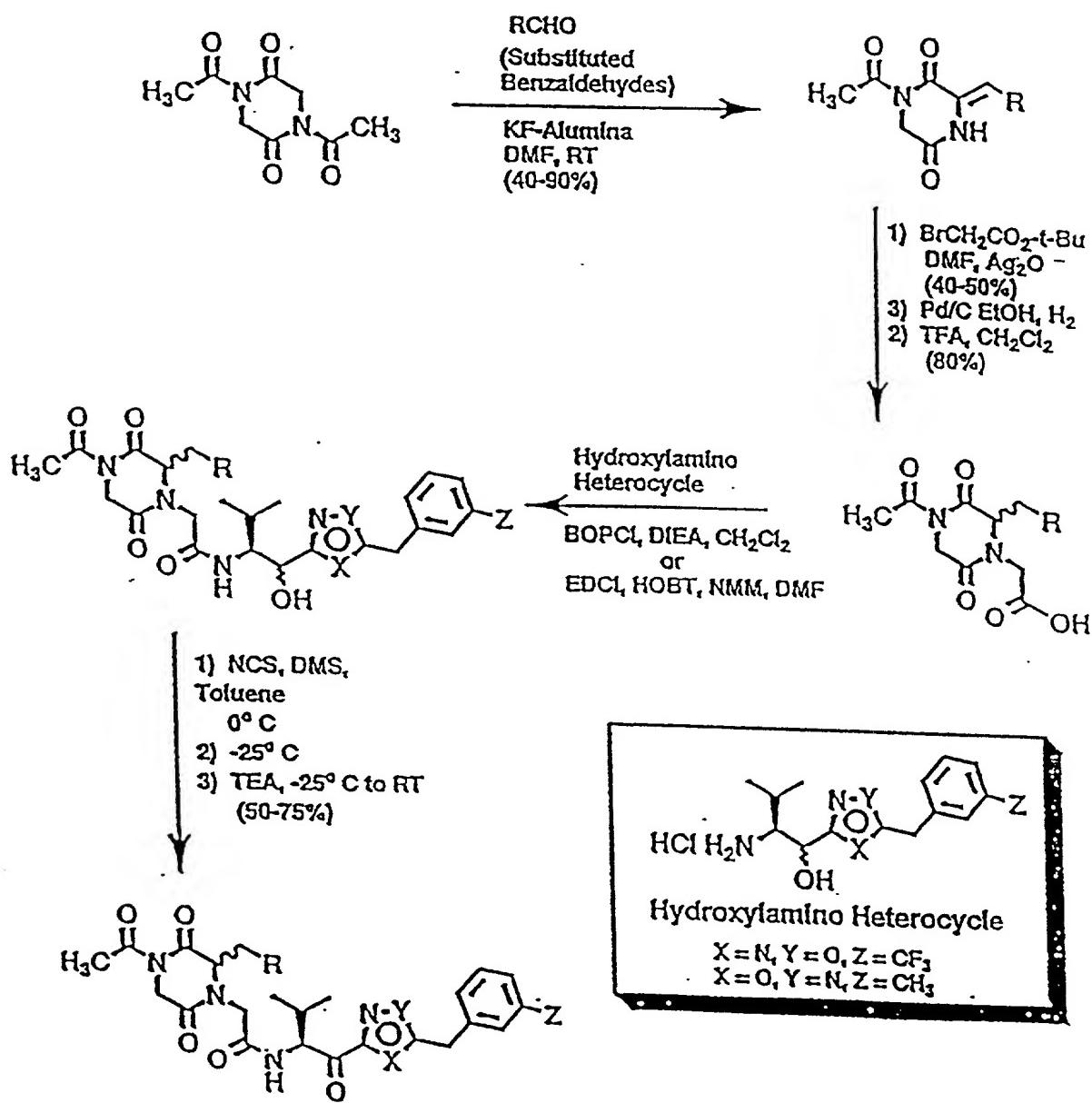


Figure 21

Synthetic Scheme for Hydantoin Based Inhibitors

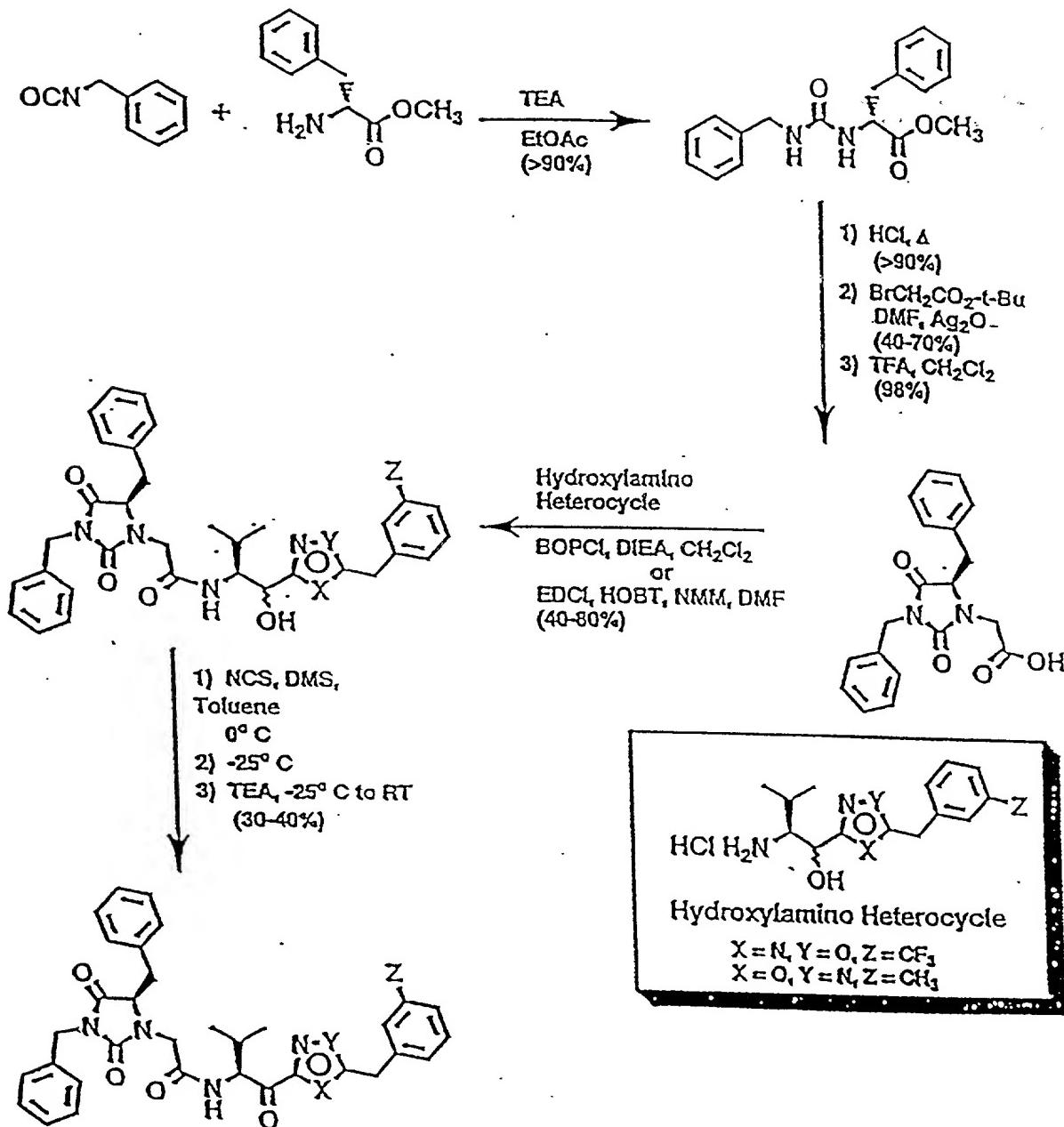


Figure 22

General Synthetic Scheme for Hydantoin Based Inhibitors

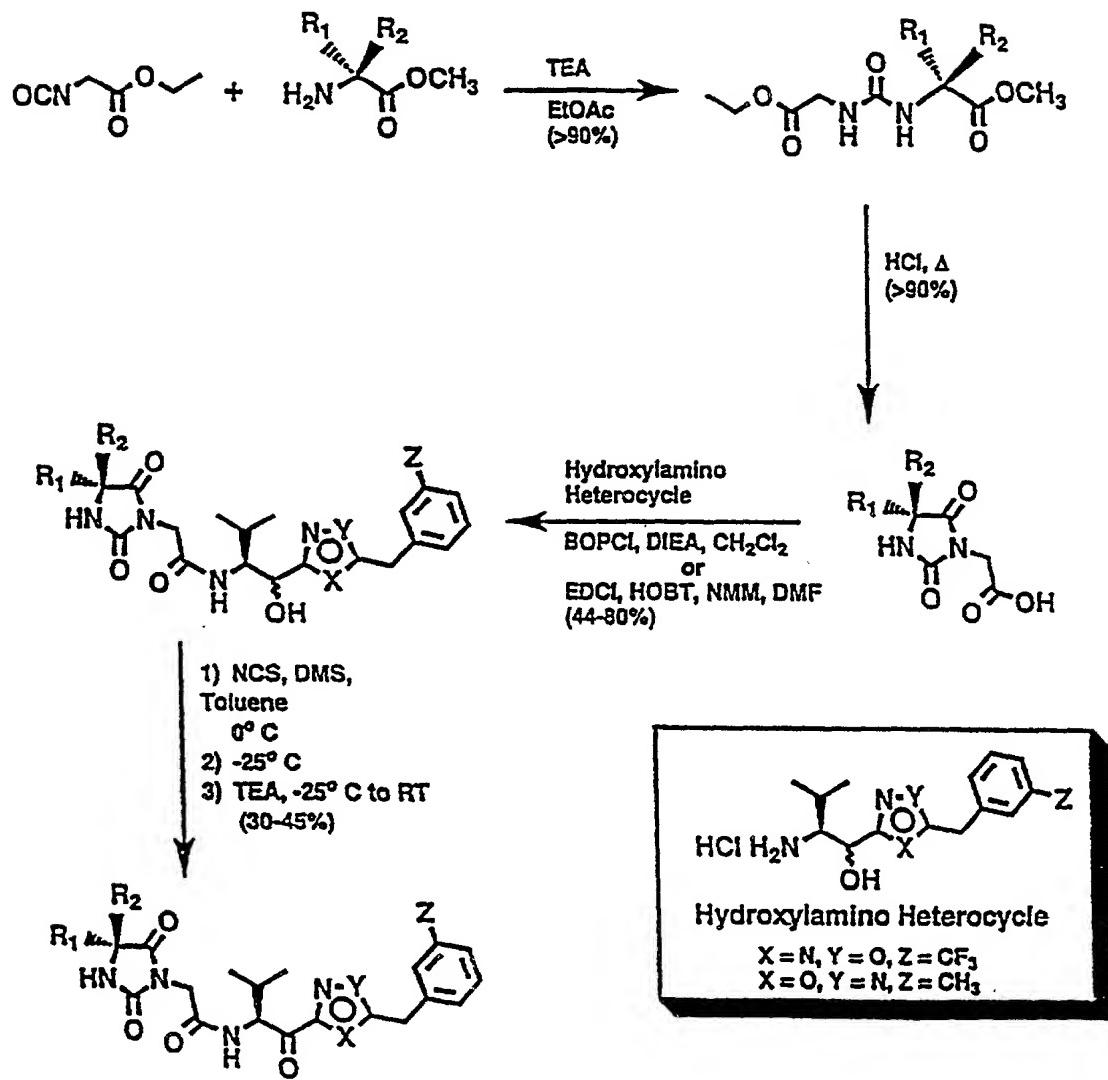
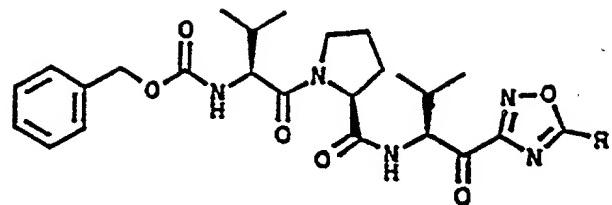
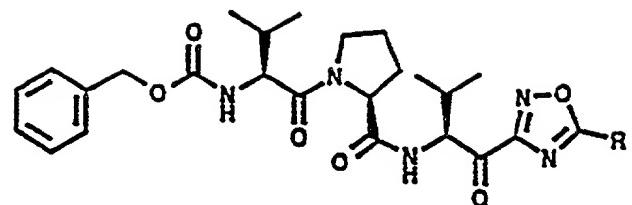


Figure 23



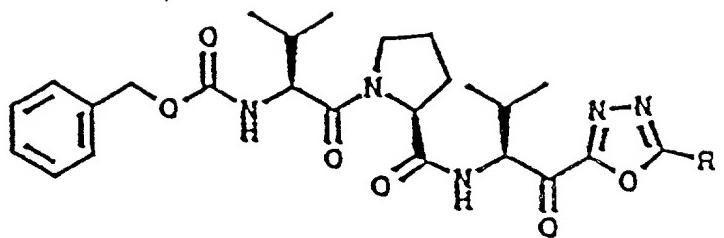
CE#	R	K_I (nM)	CE#	R	K_I (nM)
2039		2.0	2054		0.29
2042		2.5	2055		0.49
2045		1.0	2058		0.56
2048		0.36	2062		0.30
2049		0.5	2066		0.98
2052		0.37	2096		0.8
2053		0.41	2115		1.0

Figure 24



CE#	R	K_I (nM)	CE#	R	K_I (nM)
2046		9.9	2077		0.15
2047		3.8	2078		1.05
2050		1.84	2092		6.3
2057		0.38	2103		12.4
2069		4.4	2119		7.7
2073		0.24	2152		0.24
2076		1.46			

Figure 25



CE#	R	K_I (nM)
2072		0.025
2074	$-\text{CH}_3$	0.99
2075		0.11
2100		0.069
2123	$-\text{N}^+$	15.1
2124		0.033

Figure 26

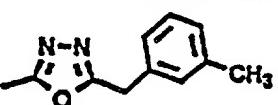
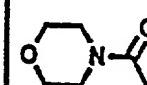
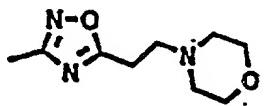
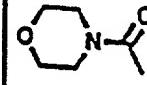
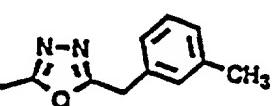
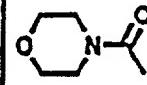
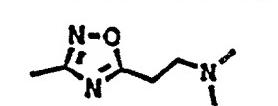
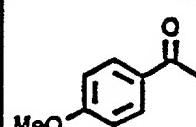
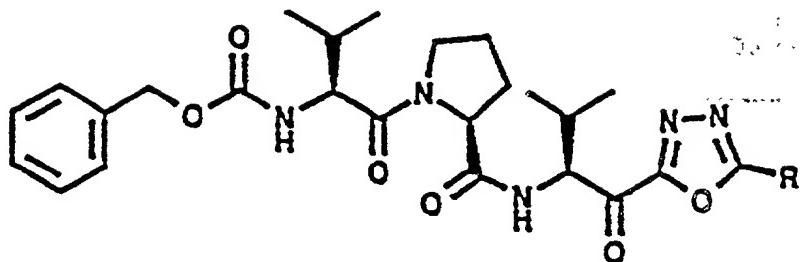
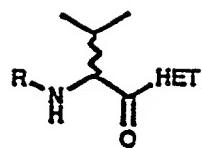
CE#	R ₁	R ₂	R ₃	HET	K _i (nM)
2083	Cbz-	CH ₃	CH ₃		73.0
2098		HPropyl	H		85.0
2104		HPropyl	H		0.33
2109		HPropyl	H		126
2110		HPropyl	H		0.13

Figure 27



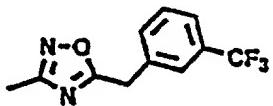
CE#	R	K _i (nM)
2072		0.025
2074	-CH ₃	0.99
2075		0.11
2100		0.069
2123		15.1
2124		0.033

Figure 28

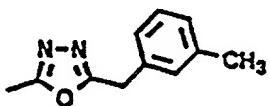


CE#	R	HET	K _I (nM)
2130		B	10.0
2132		A	24.0
2134		B	2.0
2135		A	17
2126		B	5.05
2127		A	33.9

Heterocycles:

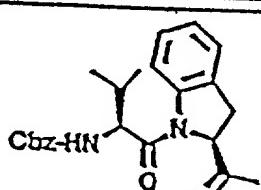
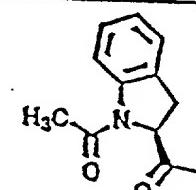
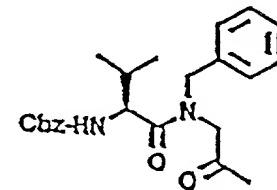
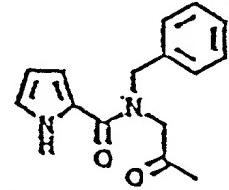
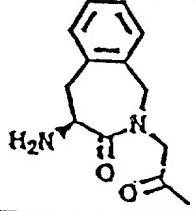


A



B

Figure 29

CE#	R	HET	K_I (nM)
2125		A	0.40
2145		B	0.038
2143		A	25.0
2056		A	0.98
2097		A	60.0
2156		A	512.0

Heterocycles:

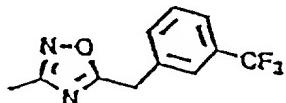
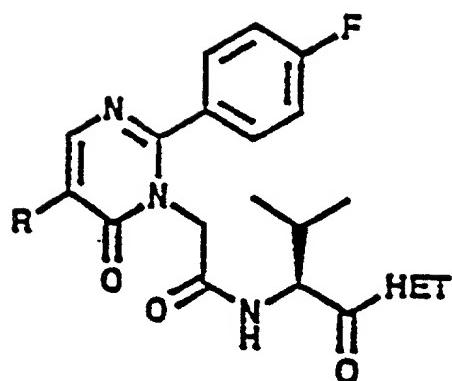
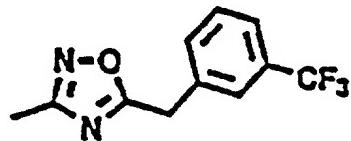


Figure 30



CE#	R	HET	K_I (nM)
2089	Cbz-NH-	A	1.5
2090	NH ₂ -	A	2.7
2095	Cbz-NH-	B	0.21
2101	NH ₂ -	B	0.64

Heterocycles:

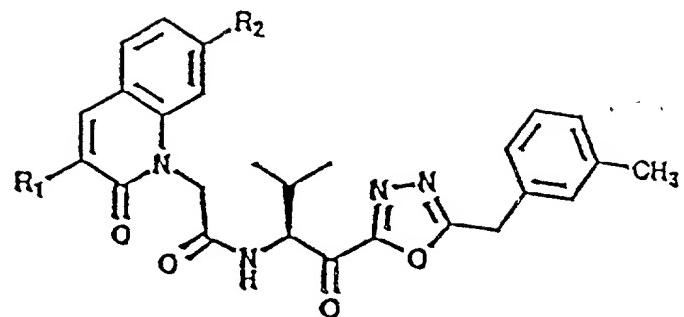


A

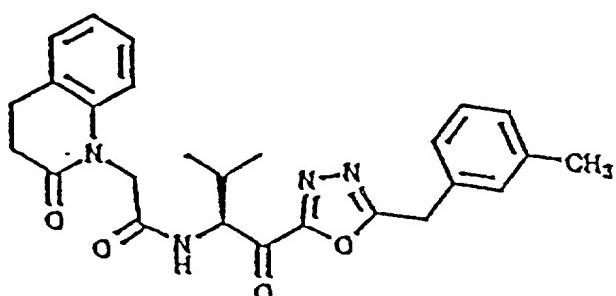


B

Figure 31

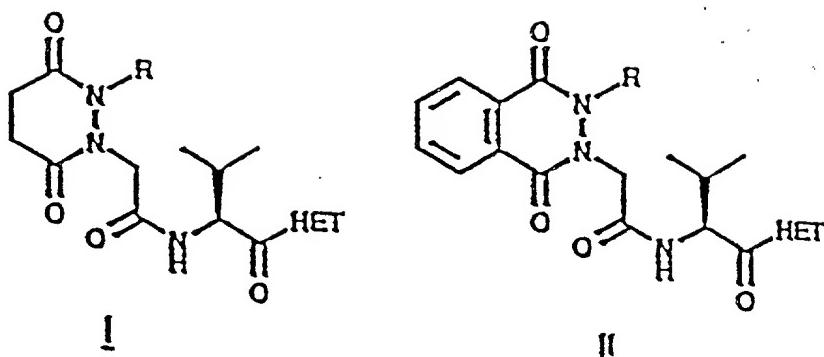


CE#	R ₁	R ₂	K _i (nM)
2107	Cbz-NH-		17.0
2108	Cbz-NH-	H	10.5
2113	H ₂ N-	H	38.8
2116		H	76.3
2117		F	587.0



CE-2088 K_i = 66.0 nM

Figure 32



CE#	R	Structure	HET	K_I (nM)
2138		I	B	294.0
2147		I	B	1590
2148		I	A	>6000
2140		II	B	204.4

Heterocycles:

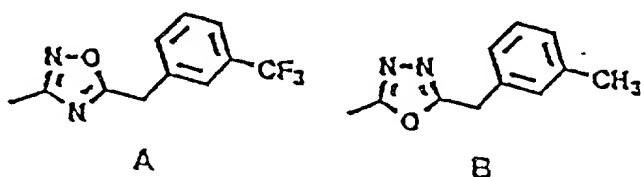
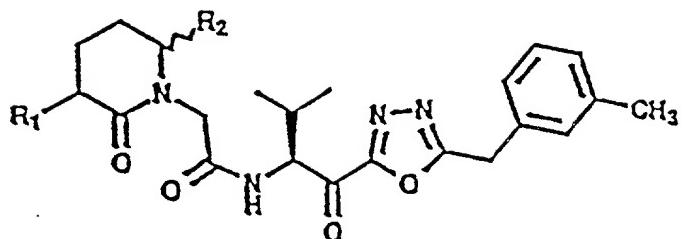
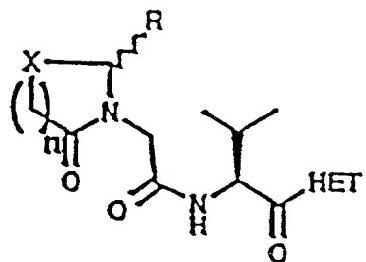


Figure 33



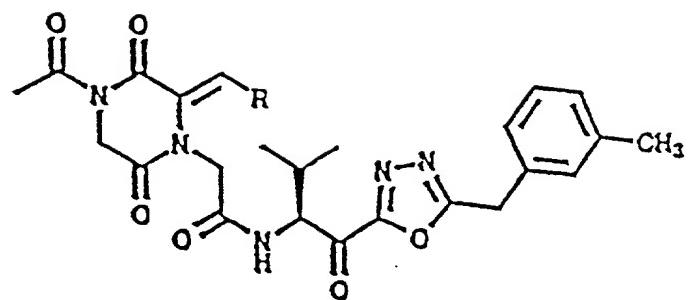
CE#	R ₁	R ₂	K _I (nM)
2079	Cbz-NH-	H	35.5
2080	H ₂ N-	H	62.0
2087	H	-F	19.8
2091		H	270.0

Figure 34



CE#	n	X	HET	R	K_I (nM)
2118	2	S			13.2
2121	1	S			28.0
2122	1	S			62.7
2136	1	SO			104.0
2137	1	SO			557.0

Figure 35



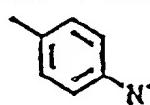
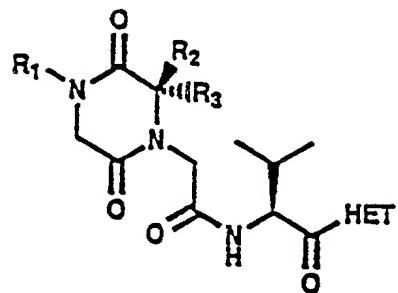
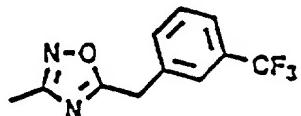
CE#	R	K_I (nM)
2099		1.9
2105		0.72
2111		20.1
2112		1.17
2114		25.1

Figure 36

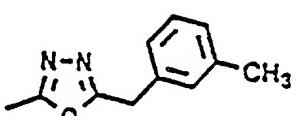


CE#	R ₁	R ₂	R ₃	HET	K _i (nM)
2084	CH ₃			A	133.0
2106	CH ₃			B	40.7
2120	CH ₃ CO-			B	50.9
2128		-H		B	64.0
2129		-H		A	300.3
2133		-H		C	33200
2139	H-			B	41.0
2144			-H	B	9.3
2146			-H	A	67.3

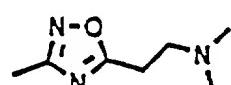
Heterocycles:



A

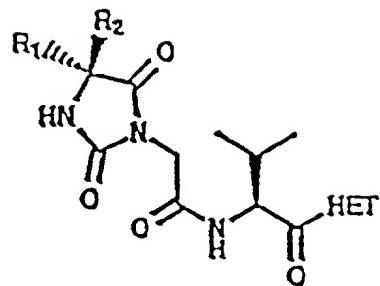


B



C

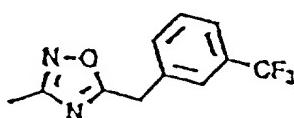
Figure 37



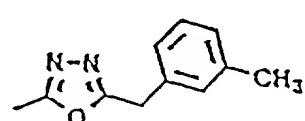
CE#	R ₁	R ₂	HET	K _I (nM)
2141		H	A	64.0
2142		H	B	8.7
2149 **		H	B	0.28
2154	H		B	10.0
2155	H		A	57.0

** Stereochemistry not definitive

Heteracycles:

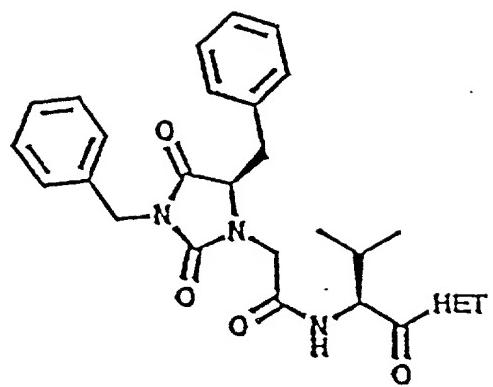


A



B

Figure 38



CE#	HET	K_I (nM)
2150		>1000
2151		60

Figure 39 - Synthesis of ONO-PO series compounds

